

REMARKS

Applicants hereby submit that the enclosures fulfill the requirements under 37 C.F.R. §1.821-1.825. The amendments in the specification merely insert sequence identifiers in the specification and replace the original Sequence Listing with an amended substitute Sequence Listing. Specifically, the amino acid sequence disclosures at page 5 and 42 have been inserted in the Sequence Listing, now SEQ ID NOs:54-57, respectively. Further, the amino acid sequences depicted in Figures 1-3, and 28-31 are included in the substitute Sequence Listing as SEQ ID NOs:58-62. Corresponding sequence identifiers have been inserted in the Brief Description of the Drawings by the present amendment. No new matter has been added.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment.

Please apply any charges or credits to Deposit Account No. 06-1050, referencing attorney docket number 06501-075001.

Respectfully submitted,

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**“Version With Markings to Show Changes Made”**

**In the specification:**

All bracketed text shown below is part of the original specification and is not meant to indicate deleted material.

Paragraph beginning at page 1, line 11, has been amended as follows:

The olfactory receptor (OR) gene family has been known as a multiple gene family encoding odorant receptors that govern the system for olfactory response in the living body. A member of the gene family was first reported to be expressed in rat olfactory neurons in 1991 (Buck L. et al. Cell 65:175-187 (1991)), and subsequently, a number of homologous genes were found across species, in canine (Permentier M. et al. Nature 355:453-455 (1992)), mouse (Ressler K.J. et al. Cell 73:597-609 (1993)), human (Selbie L.A. et al. Mol. Brain Res. 13:159-163 (1992)), catfish (Ngai J. et al. Cell 72:657-666 (1993)), and frog (Freitag J. et al. Neuron 15:1383-1392 (1995)). The receptor proteins encoded by the genes of the family have a unique seven transmembrane structure that is similar to other G protein-coupled receptor subfamilies, and their first extracellular domain contains a common [N-x-S/T] motif (x: any amino acid) which is modified by sugar. Their second and third extracellular domains, loop-1 and loop-2, respectively, are cross-linked by a disulfide bond between the conserved cysteine residues of each. The [M-A-Y-D-R-Y-L/V-A-I/V-C; SEQ ID NO:54] sequence within the second intracellular domain is another common motif predicted to be functionally important. Especially, the [D-R-Y] motif is suggested to be essential for the binding to intracellular G proteins (Rosenthal W. et al. J. Biol. Chem. 268:13030-13033 (1993); Marchese A. et al. Genomics 23:609-618 (1994)).

Paragraph beginning at page 5, line 10, has been amended as follows:

The receptor proteins of the OR gene family have a seven transmembrane type structure like other G protein-coupled receptors, and their first extracellular domains have a [N-x-S/T] motif (x: any amino acid) in common that is modified by sugar. There are conserved cysteine residues in the second (loop-1) and third (loop-2) extracellular domains that form a disulfide bond for cross-linking. Furthermore, there is a [M-A-Y-D-R-Y-L/V-A-I/V-C; SEQ ID NO:54] sequence (especially [D-R-Y] motif) in the second intracellular domain, which is suggested to be

essential for binding to the G protein (Rosenthal W. et al. J. Biol. Chem. 268:13030-13033 (1993); Marchese A. et al. Genomics 23:609-618 (1994)).

Paragraph beginning at page 5, line 32, has been amended as follows:

GTAR proteins have conserved cysteine residues in the second and third extracellular domains (loop-1 and loop-2, respectively). Furthermore, they have the [M-A-Y-D-R-Y-L/V-A-I/V-C; SEQ ID NO:54] sequence in the second intracellular domain, which is suggested to be essential for binding to G protein, as well: [V-A-Y-D-R-Y-V-A-I-C; SEQ ID NO:55] in GTAR14-1 protein, and [M-A-Y-D-R-Y-L-A-I-C; SEQ ID NO:56] in all the others.

Paragraph beginning at page 28, line 31, has been amended as follows:

OLF1 for human olfactory receptor 1 (GenBank Accession# U56420; SEQ ID NO:58); OLF2 for human olfactory receptor 2 (GenBank Accession# L35475; SEQ ID NO:59); OLF3 for human olfactory receptor 3 (GenBank Accession# L56421; SEQ ID NO:60); 14-1 for GTAR14-1 (SEQ ID NO:4); and 14-2 for GTAR14-2 (SEQ ID NO:61) (pseudogene).

Paragraph beginning at page 29, line 3, has been amended as follows:

OLF1 for human olfactory receptor 1 (GenBank Accession# U56420; SEQ ID NO:58); OLF2 for human olfactory receptor 2 (GenBank Accession# L35475; SEQ ID NO:59); OLF3 for human olfactory receptor 3 (GenBank Accession# L56421; SEQ ID NO:60); and 14-3 for GTAR14-3 (SEQ ID NO:5).

Paragraph beginning at page 29, line 12, has been amended as follows:

OLF1 for human olfactory receptor 1 (GenBank Accession# U56420; SEQ ID NO:58); OLF2 for human olfactory receptor 2 (GenBank Accession# L35475; SEQ ID NO:59); OLF3 for human olfactory receptor 3 (GenBank Accession# L56421; SEQ ID NO:60); 14-4 for GTAR14-4 (SEQ ID NO:62) (pseudogene); and 14-5 for GTAR14-5 (SEQ ID NO:6).

Paragraph beginning at page 29, line 16, has been amended as follows:

Figure 4 shows the nucleotide sequence of GTAR14-1 which was obtained by genomic PCR (SEQ ID NO:21). The positions of the primers used are underlined. The right-directed and left-directed arrows indicate the positions of 14-1-S1 primer, and 14-1-A1 primer, respectively.

Paragraph beginning at page 29, line 20, has been amended as follows:

Figure 5 shows the nucleotide sequence of GTAR14-3 which was obtained by genomic PCR (SEQ ID NO:22). The positions of the primers used are underlined. The right-directed and left-directed arrows indicate the positions of 14-3-S1 primer, and 14-3-A1 primer, respectively.

Paragraph beginning at page 29, line 24, has been amended as follows:

Figure 6 shows the nucleotide sequence of GTAR14-5 which was obtained by genomic PCR (SEQ ID NO:23). The positions of the primers used are underlined. The right-directed and left-directed arrows indicate the positions of 14-5-S1 primer, and 14-5-A1 primer, respectively.

Paragraph beginning at page 31, line 1, has been amended as follows:

Figure 10 shows the nucleotide sequence of the full length GTAR14-1 cDNA (SEQ ID NO:1) that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR14-1 cDNA is also indicated (SEQ ID NO:4). The amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, and -V).

Paragraph beginning at page 31, line 6, has been amended as follows:

Figure 11 shows the nucleotide sequence of the full length GTAR14-1 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE, continued from Figure 10 (SEQ ID NO:1). The amino acid sequence encoded by the GTAR14-1 cDNA is also indicated (SEQ

ID NO:4). The amino acid sequences predicted to be a transmembrane domain are underlined (TM-VI and -VII).

Paragraph beginning at page 31, line 11, has been amended as follows:

Figure 12 shows the nucleotide sequence of the full length GTAR14-3 cDNA (SEQ ID NO:2) that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR14-3 cDNA is also indicated (SEQ ID NO:5). Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, and -V).

Paragraph beginning at page 31, line 16, has been amended as follows:

Figure 13 shows the nucleotide sequence of the full length GTAR14-3 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE, continued from Figure 12 (SEQ ID NO:2). The amino acid sequence encoded by the GTAR14-3 cDNA is also indicated (SEQ ID NO:5). Amino acid sequences predicted to be a transmembrane domain are underlined (TM-VI and -VII).

Paragraph beginning at page 31, line 21, has been amended as follows:

Figure 14 shows the nucleotide sequence of the full length GTAR14-5 cDNA (SEQ ID NO:3) that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR14-5 cDNA is also indicated (SEQ ID NO:6). Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, and -IV).

Paragraph beginning at page 31, line 26, has been amended as follows:

Figure 15 shows the nucleotide sequence of the full length GTAR14-5 cDNA that was obtained by integrating the products of 5'-RACE and 3'-RACE, continued from Figure 14 (SEQ ID NO:3). The amino acid sequence encoded by the GTAR14-5 cDNA is also indicated (SEQ ID NO:6). [minAo] Amino acid sequences predicted to be a transmembrane domain are underlined (TM-V, -VI, and -VII).

Paragraph beginning at page 31, line 31, has been amended as follows:

Figure 16 shows the nucleotide sequence of GTAR11-1 which was obtained by genomic PCR (SEQ ID NO:50). The positions of the primers used are underlined. The right-directed and left-directed arrows indicate the positions of 11-1-S2 primer, and 11-1-A3 primer, respectively.

Paragraph beginning at page 31, line 35, has been amended as follows:

Figure 17 shows the nucleotide sequence of GTAR11-2 which was obtained by genomic PCR (SEQ ID NO:51). The positions of the primers used are underlined. The right-directed and left-directed arrows indicate the positions of 11-2-S2 primer, and 11-2-A2 primer, respectively.

Paragraph beginning at page 32, line 3, has been amended as follows:

Figure 18 shows the nucleotide sequence of GTAR11-3 which was obtained by genomic PCR (SEQ ID NO:52). The positions of primers used are underlined. The right-directed and left-directed arrows indicate the positions of 11-3-S2 primer, and 11-3-A2 primer, respectively.

Paragraph beginning at page 32, line 7, has been amended as follows:

Figure 19 shows the nucleotide sequence of GTAR11-4 which was obtained by genomic PCR (SEQ ID NO:53). The positions of the primers used are underlined. The right-directed and left-directed arrows indicate the positions of 11-4-S2 primer, and 11-4-A2 primer, respectively.

Paragraph beginning at page 33, line 35, has been amended as follows:

Figure 24 shows the nucleotide sequence of the GTAR11-1 cDNA (SEQ ID NO:24) that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR11-1 cDNA is also indicated (SEQ ID NO:28). Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, -V, -VI, and -VII).

Paragraph beginning at page 34, line 4, has been amended as follows:

Figure 25 shows the nucleotide sequence of the GTAR11-2 cDNA (SEQ ID NO:25) that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR11-2 cDNA is also indicated (SEQ ID NO:29). Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, -V, -VI, and -VII).

Paragraph beginning at page 34, line 9, has been amended as follows:

Figure 26 shows the nucleotide sequence of the GTAR11-3 cDNA (SEQ ID NO:26) that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR11-3 cDNA is also indicated (SEQ ID NO:30). Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, -V, -VI, and -VII).

Paragraph beginning at page 34, line 14, has been amended as follows:

Figure 27 shows the nucleotide sequence of the GTAR11-4 cDNA (SEQ ID NO:27) that was obtained by integrating the products of 5'-RACE and 3'-RACE. The amino acid sequence encoded by the GTAR11-4 cDNA is also indicated (SEQ ID NO:31). Amino acid sequences predicted to be a transmembrane domain are underlined (TM-I, -II, -III, -IV, -V, -VI, and -VII).

Paragraph beginning at page 34, line 19, has been amended as follows:

Figure 28 shows comparison of the amino acid sequences among known human olfactory receptors and GTAR11-1. Shadowed residues are shared by at least three proteins out of four. Dotted residues are matched in all four proteins. The N residue of the [N-x-S/T] motif (x, any amino acid residue) that is modified by sugar, conserved cysteine residues that form a disulfide bond required for cross-linking, and the D-R-Y sequence in the [M-A-Y-D-R-Y-L/V-A-I/V-C; SEQ ID NO:54] motif in the second intracellular domain, which is suggested to be essential for the binding to intracellular G proteins, are underlined. Abbreviations are as follows:

OLF1 for human olfactory receptor 1 (GenBank Accession# U56420; SEQ ID NO:58);  
OLF2 for human olfactory receptor 2 (GenBank Accession# L35475; SEQ ID NO:59); OLF3 for

human olfactory receptor 3 (GenBank Accession# L56421; SEQ ID NO:60); and 11-1 for GTAR11-1 (SEQ ID NO:28).

Paragraph beginning at page 34, line 33, has been amended as follows:

Figure 29 shows comparison of the amino acid sequences among known human olfactory receptors and GTAR11-2. Dotted residues are matched in all three proteins. The N residue of [N-x-S/T] motif (x, any amino acid residue) that is modified by sugar, conserved cysteine residues that form a disulfide bond required for cross-linking, and the D-R-Y sequence in [M-A-Y-D-R-Y-L/V-A-I/V-C; SEQ ID NO:54] motif in the second intracellular domain, which is suggested to be essential for the binding to intracellular G proteins, are underlined.

Abbreviations are as follows:

OLF2 for human olfactory receptor 2 (GenBank Accession# L35475; SEQ ID NO:59);  
OLF3 for human olfactory receptor 3 (GenBank Accession# L56421; SEQ ID NO:60); and 11-2 for GTAR11-2 (SEQ ID NO:29).

Paragraph beginning at page 35, line 9, has been amended as follows:

Figure 30 shows comparison of the amino acid sequences among known human olfactory receptors and GTAR11-3. Dotted residues are matched in all three proteins. The N residue of [N-x-S/T] motif (x, any amino acid residue) that is modified by sugar, conserved cysteine residues that form a disulfide bond required for cross-linking, and the D-R-Y sequence in [M-A-Y-D-R-Y-L/V-A-I/V-C; SEQ ID NO:54] motif in the second intracellular domain, which is suggested to be essential for the binding to intracellular G proteins, are underlined.

Abbreviations are as follows:

OLF2 for human olfactory receptor 2 (GenBank Accession# L35475; SEQ ID NO:59);  
OLF3 for human olfactory receptor 3 (GenBank Accession# L56421; SEQ ID NO:60); and 11-3 for GTAR11-3 (SEQ ID NO:30).

Paragraph beginning at page 35, line 21, has been amended as follows:

Figure 31 shows comparison of the amino acid sequences among known human olfactory receptors and GTAR11-4. Dotted residues are matched in all three proteins. The N residue of



[N-x-S/T] motif (x, any amino acid residue) that is modified by sugar, conserved cysteine residues that form a disulfide bond required for cross-linking, and the D-R-Y sequence in [M-A-Y-D-R-Y-L/V-A-I/V-C; SEQ ID NO:54] motif in the second intracellular domain, which is suggested to be essential for the binding to intracellular G proteins, are underlined.

Abbreviations are as follows:

OLF2 for human olfactory receptor 2 (GenBank Accession# L35475; SEQ ID NO:59);  
OLF3 for human olfactory receptor 3 (GenBank Accession# L56421; SEQ ID NO:60); and 11-4  
for GTAR11-4 (SEQ ID NO:31).

Paragraph beginning at page 41, line 33, has been amended as follows:

When members of known olfactory receptor (OR) gene family are structurally compared one another, they are found to share a high homology in the second and seventh transmembrane domains at the amino acid sequence level. Accordingly, among these two domains, the present inventors chose a conserved amino acid sequence [LHTPMYFFLSNLSF; SEQ ID NO:57] within the second transmembrane domain for query in BLAST search on the GenBank High Throughput Genomic Sequence (htgs) database, and tried to find a sequence of a novel useful gene belonging to the OR gene family. BLAST search was performed using default values of the TblastN (Ver.2.0.5) program. Besides detecting many sequences containing a known OR genes as a positive control, multiple human genomic sequences having a high structural homology to known OR genes were found. These sequences are found in a sequence of BAC clone originating from human chromosome 11 (GenBank Accession# AC002556), and show about 30 to 40% homology to known human olfactory receptor 1 (OLF1), OLF2, and OLF3 at the amino acid sequence level. Based on the results of analysis of gene expression pattern as described below and prediction of function, the four discovered genes were named G protein-coupled T-cell Activating Receptor 11-1 (GTAR11-1), G protein-coupled T-cell Activating Receptor 11-2 (GTAR11-2), G protein-coupled T-cell Activating Receptor 11-3 (GTAR11-3), and G protein-coupled T-cell Activating Receptor 11-4 (GTAR11-4), respectively.